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14. ABSTRACT

Systemic lupus erythematosus (lupus) is a potentially deadly systemic autoimmune disease that disproportionately afflicts women and African-Americans. This project is designed to discover genes that increase the risk of lupus in African-American. Our goal was to expand the genotyping density by genotyping a subset of our African-American lupus cases and controls on the OMNI-1S platform and then to exploit this genotyping with sequencing and follow up genotyping in an effort to identify the genes that alter disease risk. This past year we abandoned our hope of genotyping the control samples from Detroit and instead found and have already genotyped 3000 African-American controls on the OMNI-Express. (These reagents were purchased by our collaborator.) At this point the genotyping is completed and we are working on the quality control and data analysis. As we work through the remaining issues (population stratification, imputation, and detailed exploration of positive findings) we are hopeful to be composing our genome wide association study manuscript in the months to come and then turn our attention to the follow up studies with sequencing data and follow up genotyping.

15. SUBJECT TERMS
Lupus, African-American, Genome Wide Association Study (GWAS), genetic association, genetic susceptibility, candidate gene association study, genotyping

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1. Abstract/Introduction (SF298 requirement)

Systemic lupus erythematosus (lupus) is a potentially deadly systemic autoimmune disease that disproportionately afflicts women and African-Americans. This project is designed to discover genes that increase the risk of lupus in African-American. Our goal was to expand the genotyping density by genotyping a subset of our African-American lupus cases and controls on the OMNI-1S platform and then to exploit this genotyping with sequencing and follow up genotyping in an effort to identify the genes that alter disease risk. This past year we abandoned our hope of genotyping the control samples from Detroit and instead found and have already genotyped 3000 African-American controls on the OMNI-Express. (These reagents were purchased by our collaborator.) At this point the genotyping is completed and we are working on the quality control and data analysis. As we work through the remaining issues (population stratification, imputation, and detailed exploration of positive findings) we are hopeful to be composing our genome wide association study manuscript in the months to come and then turn our attention to the follow up studies with sequencing data and follow up genotyping.

2. Body

Since the population history of African ancestry appears to reach back in time much further to the most recent small founder population (~200,000 years) than the other major human ancestries (<50,0000 years for Asian, European, or Amerindian), the extent of linkage disequilibrium is much lower in population samples of African ancestry. This means that the usual approach for finding genetic association using haplotype block tagged markers will be less successful in this ancestry. One way to partially compensate for this problem is to increase marker density, which is what we are funded to do in this project in our genetic study of systemic lupus erythematosus (lupus).

Lupus in African-Americans is more severe and more deadly than in other populations, and especially so compared to European-Americans. Indeed, lupus afflicts women ten times more frequently than men with a strong tendency to strike during the child-bearing years and is relatively common among the Active Duty Military (1).

3. Key Research Accomplishments

- Our DOD project is a component of a larger project to more fully characterize African-American genetic association with lupus by genome wide association. We hope to have completed genotyping. We are deep in to the evaluation of the data, removing markers and samples that appear to have the potential of artifact from stratification, poor clustering, batch effects, reduced marker calling, and disproportions in controls. At this point we are working with data from all sources from 7,300 DNA samples. Of these this project contributed 574 controls and 1,590 cases evaluated on the OMNI-1S platform. These results are

complemented by genotyping from 434 controls and 2,359 cases on the OMNI-1 platform. (Together, the OMNI-1S and OMNI-1 are almost equivalent to the OMNI-2.5.) We have 1,536 controls available with genotyping from the OMNI-2.5 platform, available from dbGaP. In addition, we genotyped 3,985 African-American controls on the OMNI-Express platform in a collaboration with Mt. Sinai in New York City. The merged data provide nearly 3 million single nucleotide markers from 7,300 subjects for a dataset that will have the power for inquiry equivalent to nearly 22 billion genotypes when the imputation across the platforms is completed.

- Certainly, the analysis of these data is an enormous challenge, but is progressing with an anticipated completion before January 2013. Preliminary analyses support not only finding many genetic associations that have been identified in the Asian and European genome wide studies of lupus, but also a few genes that are novel, such as IKBKB for an association with African-American lupus. We hesitate to present these here since we are still culling to artifacts from the results. For example, one very promising association was shown to be almost exactly duplicated on the Y chromosome, which meant that the result was confounded by sex because there were a higher proportion of males in the controls than in the cases. Once the result was adjusted for sex, the association disappeared.

- While the analysis of the genome wide data is being completed, we will assemble data from DNA sequencing in African Americans so that imputation of the exome can be obtained for the genetic associations. Also, as soon as we complete the association, then we will organize targeted genotyping to fine map the areas of greatest interest, as presented in our previously submitted budget.

- Studies published this past year have presented novel findings in a variety of settings. Our control data were used in a study of sarcoidosis (2), showing how the data collected for one project can be a benefit in another, saving precious resources. The location of the responsible variant for lupus risk associated with ITGAM was identified because the African ancestry has low linkage disequilibrium in this genomic region (3). Gene-gene and gene-sex interactions along with phenotypic variation with genetic association remain fascinating aspects of this genetic approach (4,5,8,9). Indeed, these same African-American cases, which are ~16% European ancestry, showed association with a subset of the apparently associated genes taken from a genome wide association study in European ancestry.

- We look forward to completing this project and hope that we will have a comparatively productive report next year.

4. Reportable Outcomes

1. Adrianto I, Lin CP, Hale JJ, Levin AM, Datta I, Parker R, Adler A, Kelly JA, Kaufman KM, Lessard CJ, Moser KL, Kimberly RP, Harley JB, Iannuzzi MC, Rybicki BA, and Montgomery CG. (2012) Genome-wide association study of african and European americans implicates multiple shared and ethnic specific Loci in sarcoidosis susceptibility, *PLoS One 7*, e43907. PMCID: PMC3428296.

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3. Hughes T, Adler A, Kelly JA, Kaufman KM, Williams AH, Langefeld CD, Brown EE, Alarcon GS, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Boackle SA, Stevens AM, Reveille JD, Sanchez E, Martin J, Niewold TB, Vila LM, Scofield RH, Gilkeson GS, Gaffney PM, Criswell LA, Moser KL, Merrill JT, Jacob CO, Tsao BP, James JA, Vyse TJ, Alarcon-Riquelme ME, Harley JB, Richardson BC, and Sawalha AH. (2012) Evidence for gene-gene epistatic interactions among susceptibility loci for systemic lupus erythematosus, *Arthritis Rheum 64*, 485-492. PMCID: PMC3268866.

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5. Conclusions

The planned project to expand the density and number of markers in a case-control study of African-American systemic lupus erythematosus is proceeding as planned.

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7. Appendices

NONE.